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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/700,922	11/03/2003	Johanna Bergmann	830006-2000	5900

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EXAMINER	
EMCH, GREGORY S	
ART UNIT	PAPER NUMBER
1649	
MAIL DATE	DELIVERY MODE
08/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/700,922	BERGMANN ET AL.	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8 and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Claims 8 and 9 have been amended as requested in the amendment filed on 14 June 2007. Following the amendment, claims 8 and 9 are pending in the instant application.

Claims 8 and 9 are under examination in the instant office action.

Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Specification

A substitute specification consistent with the claims is required pursuant to 37 CFR 1.125(a) because as demonstrated in the sequence listing filed on 14 October 2004, the sequence identifiers have been exchanged such that identification of the proteins and nucleic acids of the invention is now inconsistent with the remainder of the specification. This is considered a clerical error as both sequence listings (submitted 14 October 2004 and 03 November 2003) appear to contain the same molecules. Thus, it is suggested that Applicants amend the sequence identifiers throughout the specification to reflect the most recent sequence listing submitted 14 October 2004 Applicants may do this either in the form of amendment with replacement paragraphs or amendment with a substitute specification.

A substitute specification must not contain new matter. The substitute specification must be submitted with markings showing all the changes relative to the immediate prior version of the specification of record. The text of any added subject matter must be shown by underlining the added text. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. The text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived. An accompanying clean version (without markings) and a statement that the substitute specification contains no new matter must also be supplied. Numbering the paragraphs of the specification of record is not considered a change that must be shown.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The enablement rejection of claims 8 and 9 under 35 U.S.C. 112, first paragraph is maintained for reasons of record and as set forth below. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

In the reply filed 14 June 2007, Applicants assert that undue experimentation does not necessarily follow from a lack of examples in the specification and that an applicant need not describe all actual embodiments of a claimed invention. Applicants assert that they "used a procedure which they had successfully used to find alternative genes, which are putative causative factors of other 'genetic diseases', to search for such genes which might segregate with Alzheimer's disease, within the locus encoding the entire APP gene on chromosome 21 and the regions that flank the gene...Therefore, based upon the Applicants' disclosure, one of skill in the art would believe that ALZAS proteins are not mere markers but rather causative agents of Alzheimer's disease or associated diseases." Applicants assert that their data strongly supports involvement of ALZAS molecules in the etiology of Alzheimer's disease. For example, Applicants allege that "the specification also discloses that affinity purification of ALZAS on columns of anti-ALZAS-sepharose columns of patients indicate that the ALZAS protein is bound to human immunoglobulin fragments in Alzheimer's disease patients. This indicates that ALZAS is modulated by the immune systems in Alzheimer's disease victims, and may be a target for complement derived destruction."

Applicants' arguments have been fully considered and are not found persuasive.

The Examiner agrees that undue experimentation does not necessarily follow from a lack of working examples in the specification and that an applicant need not describe all actual embodiments of a claimed invention. However, in the instant case, Applicants have not described any of the actual embodiments such that the skilled artisan can practice the claimed invention without undue experimentation. As stated previously, no actual therapeutic data is disclosed in the specification from human patients or from an art-accepted animal model for AD or associated diseases.

It is well known in the art that neurodegenerative disorders, such as Alzheimer's disease have different symptoms, pathologies, and etiologies. Multiple sclerosis is an autoimmune disease characterized by multiple regions of demyelination and inflammation along axonal pathways and an upregulation of inflammatory factors and cells in the cerebrospinal fluid (Purves et al. Eds, Neuroscience, 2001, Sinauer Associates, Inc., 2nd Edition, p. 75). Parkinson's disease is characterized by defects in motor function, e.g. resting tremor, rigidity of extremities and neck, shortened steps with minimal arm swinging, and stooped posture, due to the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (Purves et al., p. 403). Huntington's disease is characterized by the gradual onset of defects in motor behavior, cognition, and movement, e.g. mood alterations, dementia, memory deficits, and rapid, jerky motions with no clear purpose resulting from a profound and selective atrophy of the caudate, putamen, and some degeneration of the frontal and temporal cortices (Purves et al., p. 400). Amyotrophic lateral sclerosis is characterized by the slow but

inevitable degeneration of α motor neurons in the spinal cord ventral horns and brainstem and neurons in the motor cortex leading to eventual paralysis and death (Purves et al., p. 367). Manic depression is characterized by patients experiencing alternating episodes of depression and euphoria and is defined clinically by an abnormal sense of sadness, despair, bleak feelings about the future, disordered eating and sleeping, poor concentration, inappropriate guilt, and diminished sexual interest (Purves et al, p. 640). Also, despite evidence for a genetic predisposition and an increased understanding of the brain areas involved, the cause of this condition remains unknown (Purves et al., p.641). Treatment for such a disorder includes tricyclic antidepressants, monoamine oxidase inhibitors and selective serotonin reuptake inhibitors. Alzheimer's disease involves an initial loss of recent memory function and attention, followed by failure of language skills, visual-spatial orientation, abstract thinking, and judgment and alterations of personality (Purves et al., p. 678). The histopathology involves collections of neurofibrillary tangles and senile plaques and diffuse loss of neurons. Epilepsy can be caused by a variety of acute or congenital factors, including cortical damage from trauma, stroke, tumors, failure of the cortex to develop properly, congenital vascular malformations, and autoimmune conditions wherein antibodies to glutamate receptors contribute to the pathology (Purves et al., p. 554).

Although Applicants have amended the claims to delete reference to "prevent" and "stop" initiation and progression of AD and associated diseases, passive vaccination still encompasses preventing or prophylaxis. The Office broadly interprets

claims reciting vaccination as encompassing the prevention of a disease or ailment, and it is therefore irrelevant that the claims do not explicitly recite "prevention" or "total prevention" as asserted by Applicants. The claims are thus interpreted as being drawn to prevention of AD or associated disease in any given individual, because the claims encompass patients at risk of having the disease. As the etiological cause has not yet been clearly defined for all such diseases, e.g. Alzheimer's disease, any given individual is potentially at risk of developing the disease and the patient population therefore includes *everyone*.

Furthermore, the art teaches that no effective prevention or cure exists for epilepsy, although some successful therapy is achieved with altering ion channel conductance, or with more severe cases, removal of cerebral tissue (Purves et al., p.555). Bridler et al. (Swiss Med Wkly. 2003 Feb 8;133(5-6):63-76) teaches that even with the most successful treatment for schizophrenia, i.e., antipsychotic therapy, a significant number of patients relapse or develop partial or full resistance (p.64). As stated previously, there is no known cure, treatment or preventative measure for Alzheimer's disease and related diseases, as evidenced by Vickers (cited previously) who teaches, "Alzheimer's disease (AD) is the leading cause of age-related dementia and is set to markedly increase in incidence with the gradual aging of the populations in both developed and developing nations. Along with most brain diseases and conditions, there is no effective treatment currently available to reverse, slow down or prevent its course." Branas et al. teaches that there is no cure for multiple sclerosis and that alleviation of symptoms is the cornerstone of care (Health Technol Assess, 2000;

4(27): pp.1-4, first paragraph). Oksenberg teaches that ideal therapy for multiple sclerosis is to reverse established disease and prevent further progression (West J Med. 1994 Sep; 161(3): 255-9, abstract). Since the claims encompass methods reciting various disease states and given the art-recognized unpredictability of treatment protocols and the lack of guidance presented in the specification, it would require undue experimentation to provide passive immunization against all of these disease states with the instantly claimed antibodies.

Applicants extrapolate the data set forth in the specification to assert that the administration of an antibody of the invention is capable of effecting prophylaxis or treatment of Alzheimer's disease. However, it is noted that the instant specification only demonstrated correlative data in human tissue of patients *that have already demonstrated* disease pathology. While prophetic examples of prophylactic treatment are noted, there is no evidence (either in the specification or in the relevant art at the time of filing) to suggest that administration of the claimed antibodies would provide effective prophylaxis to a subject at risk of developing an AD-related pathology (or pathology associated with any disease). The art teaches that the ALZAS protein contains the Aβ 1-42 fragment, the APP transmembrane signal, and a unique 12 amino acid c-terminal, which is not present in any known allele of the APP gene (Kienzl et al. J Neural Transm Suppl. 2002;(62):87-95). The art recognizes that the normal function of Aβ is not fully characterized. Perez et al. (J Neurosci. 1997 Dec 15;17(24):9407-14) teaches that cell-associated neuronal beta-Amyloid precursor protein (betaPP) contributes to neuron viability, axonogenesis, and arborization and that betaPP

secretory products modulate axon growth, dendrite branching, and dendrite numbers (entire document, e.g., abstract). Liu et al. (Proc Natl Acad Sci U S A. 1998 Oct 27;95(22):13266-71) teaches that Aβ and submicromolar concentrations of free cholesterol alter the trafficking of a population of intracellular vesicles that are involved in the transport of the reduced form of the tetrazolium dye 3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT formazan), the formation of which is a widely used cell viability assay. In addition, the reference teaches that Aβ decreases cholesterol esterification and changes the distribution of free cholesterol in neurons (entire document, e.g., abstract). So while there may be a pathogenic function of Aβ when overexpressed within neuronal cells, the normal physiologic role of Aβ appears to be critical to the maintenance and survival of neurons. Accordingly, the consequences of administering prophylactic agents to normal, healthy individuals to modify or reduce Aβ levels would be highly unpredictable.

While it is possible to greatly reduce the incidence of certain conditions or occurrences, such as reducing the risk of heart disease through proper diet and exercise, or "preventing" pregnancy with correctly used birth control, prophylactic agents or therapies aimed at reducing the risk of neurodegenerative disease have fared poorly, thus evidencing unpredictability with respect to the prophylactic application of the currently claimed invention. For example, for many years it was believed that reduced estrogen levels in post-menopausal women were the contributing factor to the observed higher rates of Alzheimer's disease in women. Hormone replacement therapy (HRT, and in particular, estrogen replacement) was thus touted as a therapy to reduce the

incidence of developing Alzheimer's disease (AD) in these women. However, recent studies indicate that there is no significant benefit to of HRT in reducing the occurrence of AD in prophylactically treated elderly women (for review, see Casadesus et al. Drugs in R&D, 2006; 7(3): 187-193). Thus, while the logic behind HRT as a prophylactic therapy may have been sound, the art clearly indicates the unpredictability of prophylaxis of neurodegenerative disease and Alzheimer's disease in particular.

The skilled artisan would clearly require additional guidance for the effective use of such prophylactic methods in patients at risk of such a disease. Accordingly, the complex nature of the invention would not allow the skilled artisan to predict the effects of administration of the antibodies of the invention for purposes of effecting prophylaxis in a patient that is at risk of developing AD or an associated disease. Both at the time of filing and now, effective therapy for effecting prophylaxis of neurodegenerative diseases such as Alzheimer's has eluded researchers. For example, De Lustig et al. (*Rev in Neurosciences*, 1994, 5: 213-225) report that there is still no adequate preventive (i.e, prophylactic) strategy for Alzheimer's disease pathology (p.213).

Additionally and as stated previously, the expression data presented in the specification is correlative only. Just because a biological molecule correlates with the presence of a disease does not mean it is a therapeutic target. The molecule may accumulate as a *result* of the disease and thus may not play a *causative* role or a role in disease *progression*. Applicants have not established a nexus between said data and a method of passive vaccination to prevent and stop initiation and progression, respectively, of Alzheimer's disease and other associated diseases with antibodies (or

fragments thereof) to the proteins of the invention. The fact that the specification teaches expression of a protein of the invention in samples from AD patients does not enable the skilled artisan to prevent or treat AD or any other disease. Furthermore, ALZASp2 is not present in AD samples; thus, it is unclear how an antibody to this molecule would have any use in disease treatment.

Since the claims encompass prophylaxis of various disease states with divergent symptoms and given the art-recognized unpredictability and variability of treatment protocols, the lack of any nexus established between Alzheimer's disease or associated disorders and an antibody of the invention, the lack of data or evidence supporting a prophylactic effect of the claimed immunization method, the unpredictability in the art of prophylaxis of neurodegenerative diseases, and the complex nature of the invention, it would require undue experimentation for one of skill in the art to practice the claimed invention.

Conclusion

No claims are allowed.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gregory S. Emch/

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22 August 2007

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